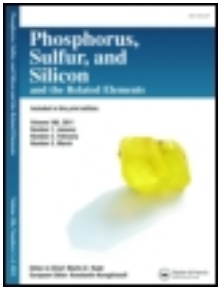

Phosphorus, Sulfur, and Silicon and the Related Elements

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ONE—POT SYNTHESIS OF PYRIDINES, THIENOPYRIDINES, PYRROLOTHIENOPYRIDINES AND (1,8) NAPHTHYRIDINES UNDER PHASE-TRANSFER CATALYSIS CONDITIONS

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ONE – POT SYNTHESIS OF PYRIDINES, THIENOPYRIDINES, PYRROLOTHIENO-PYRIDINES AND (1,8)NAPHTHYRIDINES UNDER PHASE-TRANSFER CATALYSIS CONDITIONS

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A new series of pyridines $\mathbf{2_{a,b}}$, (1,8)naphthyridines $\mathbf{3_{a,b}}$ and diazepines $\mathbf{4_{a,b}}$ were synthesized in one-pot reaction under phase-transfer catalysis conditions (PTC) starting with cyanoketene S,S-acetals **1** and cyanothioacetamide, cyanoacetamide or cyanoacetohydrazide in different molar ratios. The reaction of $\mathbf{2_a}$ with halo compounds in equimolar ratio gave thienopyridines $\mathbf{5_{a-d}}$, while on using 1:2 molar ratio afforded pyrrolothienopyridines $\mathbf{6_{a-d}}$. Also, bis thieno(1,8)naphthyridines $\mathbf{7_{a-d}}$, bis-pyrrolo (1,8)naphthyridine **9** and bis(1,6)naphthyridines $\mathbf{10_{a-c}}$ were obtained by treating (1,8)naphthyridine $\mathbf{3_a}$ with the suitable reagents.

Keywords: Naphthyridines; thienopyridines; pyrrolothienopyridines bis-thienonaphthyridines; PTC

INTRODUCTION

The synthesis of cyanoketene[1] or ketoketene S,S-acetal[2] as well as heterocyclic ketene N,N-[3–9] or N,S-acetals[5,10–14] has attracted considerable attention since these acetals are used as a versatile starting materials for the synthesis of a wide variety of fused heterocycles. As an extention of our recent studies [15–17] on the application of Phase-Transfer Catalysis conditions (PTC) in heterocyclic synthesis we report here the synthesis of some new polyfused heterocyclic systems containing pyridine or biologically active 1,8-naphthyridine[18,19] moiety starting with cyanoketene S,S-acetals[1].

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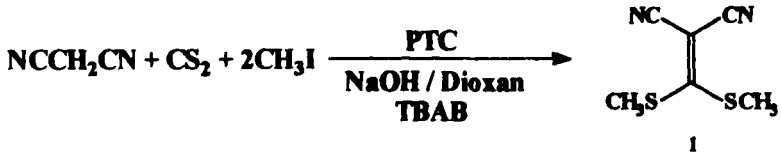
RESULTS AND DISCUSSION

Dimethylthiomethylene malononitrile **1** was obtained via reaction of malononitrile and CS_2 with two equivalents of methyl iodide in one pot reaction using PTC conditions [NaOH / dioxan / tetrabutylammonium bromide TBAB] in 97% yield [20].



1

Compound **1** was allowed to react with cyanothioacetamide or cyanoacetamide in equimolar ratio under PTC conditions [K_2CO_3 / dioxan / TBAB] to give the corresponding pyridines $\mathbf{2_{a,b}}$, while the reaction of compound **1** with the same reagents in 1:2 molar ratio using the same PTC conditions, the corresponding 1,8-naphthyridines $\mathbf{3_{a,b}}$ were obtained. The structures of the products were established by their IR, ^{1}H-NMR, MS spectral data (cf. Table I). The formation of pyridines $\mathbf{2_{a,b}}$ or 1,8-naphthyridines $\mathbf{3_{a,b}}$ was suggested to proceed via firstly, the elimination of one or two molecules of methyl mercaptan through the reaction of one or two molecules of the amide with one molecule of the substrate, then the cyclization occurs in sequent steps.

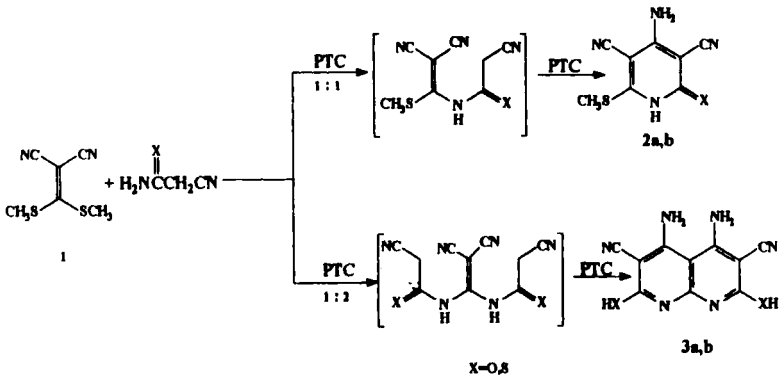


TABLE I Analytical and spectral data of the prepared compounds

Comp. No.	Reaction time h/temp. (°C)	M.P.[a] (Crys. Solvent)	Yield %	$M_F(M_w)$[b]	Analytical data calc. (Found) %				IR(Kbr) ν (cm^{-1})[c]	^{1}H-NMR (DMSO-d_6) (δppm)[d]
					C	H	N	S		
2_a	**15/80**	260[e] (dioxan)	77	$C_8H_6N_4S_2$ (222.29)	43.23 (43.48)	2.72 (2.69)	25.20 (25.42)	28.85 (28.75)	3300, 3211,3117 (NH_2, NH), 2205, 2202 (2CN), 1427 (C-SCH_3).	9.20 (br, 1H, NH), 6 20 (br, 2H, NH_2), 2.30 (s, 3H, SCH_3).
2_b	**15/65**	> 300 (dioxan)	85	$C_8H_6N_4OS$ (206.23)	46.59 46.69	2.93 (2.88)	27.17 (27.27)	15.55 (15.42)	3402, 3327, 3200 (NH_2, NH), 2204, 2200 (2CN), 1680 (C = O), 1430 (C-SCH_3)	9.10 (br, 1H, NH), 6.30 (br, 2H, NH_2), 2.50 (s, 3H, SCH_3).
3_a	**25/85**	> 300 (dioxan/ DMSO)	78	$C_{10}H_6N_6S_2$ (274.33)	43.78 (43.66)	2.20 (2.15)	30.63 (30.56)	23.38 (23.58)	3348, 3302, 3209, 3117 ($2NH_2$), 2640 (SH), 2206, 2202 (2CN).	9.80 (br, 2H, 2NH), 6.50, (br, 4H, $2NH_2$), 2.80 (s, 2H, SH).
3_b	**16/80**	> 300[e] (dioxan/ DMSO)	88	$C_{10}H_6N_6O_2$ (242.20)	49.59 (49.44)	2.50 (2.46)	34.70 (34.82)	– –	3560, 3490 (2 OH), 3321, 3220, 3175, 3120 ($2NH_2$), 2210, 2206 (2CN).	6.95 (s, 4H, $2NH_2$), 3.30 (br, 2H, 2 OH).
4_a	**17/60**	149 – 50 (ethanol)	86	$C_8H_7N_5OS$ (221.24)	43.43 43.50	3.19 (3.22)	31.65 (31.74)	14.49 (14.30)	3414, 3333, 3215 (NH_2 NH), 2206 (2CN), 1650 (C =O).	9.30–8.90 (br, 2H, 2NH), 5.50 (br, 2H, NH_2), 2.40 (d, 3H, SCH3).
4_b	**20/75**	> 300 (dioxan)	83	$C_{10}H_8N_8O_2$ (272.23)	44.12 44.08	2.96 (2.91)	41.16 (41.26)	– –	3440, 3298, 3180 ($2NH_2$, 2NH), 2220, 2199 (2CN), 1630 (C = O).	8 30–7.90 (br, 4H, 4NH), 4.90–4.60 (br, 4H, $2NH_2$).

Comp. No.	Reaction time h/temp. (°C)	M.P.[a] (Crys. Solvent)	Yield %	$M_F(M_w)$[b]	Analytical data calc. (Found) %				IR(Kbr) ν (cm^{-1})[c]	^{1}H-NMR (DMSO-d_6) (δppm)[d]
					C	H	N	S		
5_a	**7/85**	274 – 75 (dioxan/ ethanol)	72	$C_{12}H_{12}N_4O_2S_2$ (308.38)	46.74 (46.79)	3.92 (3.97)	18.17 (18.27)	20.80 (20.65)	3427, 3315, 3190 (NH2), 2208 (CN), 1650 (C = O).	6.40–6.00 (br, 4H, NH2), 3.80–3.50 (q, 2H, CH_2), 3.10 (s, 3H, SCH_3), 1.10–0.90 (t, 3H,
5_b	**4/85**	> 300 (dioxan/ ethanol)	66	$C_{10}H_7N_5S_2$ (45.66)	45.96 (45.66)	2.69 (2.66)	26.80 (26.64)	24.54 (24.68)	3422, 3373, 3329, 3217 ($2NH_2$), 2200, 2183 (2CN).	6.50 (s, 2H, NH_2), 6.10 (s, 2H, NH_2), 2.10 (s, 3H, SCH3).
5_c	**7/85**	168 – 70 (dioxan)	81	$C_{16}H_{12}N_4S_2$ (324.43)	59.34 (59.18)	3.73 (3.70)	17.27 (17.19)	19.77 (19 86)	3422, 3368, 3320, ($2NH_2$) 2204 (CN), 1630 (C = O).	7.20–6 50 (m, 5H arom.), 6.20–5.90 (br, 4H, $2NH_2$), 2.30 (s, 3H, SCH_3).
5d	**6/85**	298 – 99 (dioxan/ ethanol)	62	$C_{10}H_9N_5OS_2$ (279.34)	43.00 (43.08)	3.25 (3.30)	25.07 (25.14)	22.26 (22.12)	3447, 3330, 3280, 3175 ($3NH_2$), 2216 (CN), 1635 (C=O).	7 20 (s, 2H, NH_2), 7.10 (s, 2H, NH_2), 6.80 (s, 2H, $CONH_2$), 2.90 (s, 3H, SCH_3).
6_a	**10/80**	182 – 84 (dioxan)	68	$C_{16}H_{18}N_4O_4S_2$ (394.47)	48.72 (48.60)	4.60 (4.56)	14.20 (14.13)	16.26 (16.36)	3460, 3326, 3327, 3210 ($2NH_2$, NH) 1710 (C = O).	9.90–9.70 (br, 1H, NH), 6 80–6.50 (br, 4H, $2NH_2$), 4.00–3.70 (m, 4H, $2CH_2$), $2CH_3$).
6_b	**6/90**	> 300 (acetic acid)	61	$C_{12}H_8N_6S_2$ (300.37)	47.99 (48.02)	2.68 (2.73)	27.98 (28.00)	21.35 (21.18)	3418, 3379, 3310, 3177 ($2NH_2$, NH) 2183 (CN).	9.10–9.00 (br, 1H, NH), 7.50 (s, 2H, NH_2), 7.00 (s, 2H, NH_2), 2.90 (s, 3H, SCH_3).

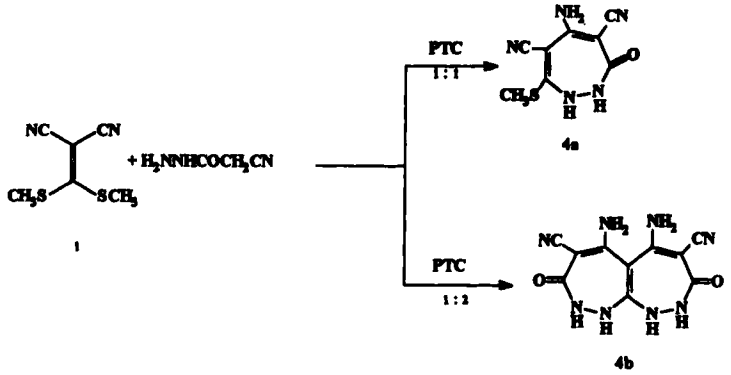
Comp. No.	Reaction time h/temp. (°C)	M.P.[a] (Crys. Solvent)	Yield %	$M_F(M_w)$[b]	Analytical data calc. (Found) %				IR(Kbr) ν (cm^{-1})[c]	^{1}H-NMR (DMSO-d_6) (δppm)[d]
					C	H	N	S		
6_c	**8/80**	193 – 95 (dioxan/ DMSO)	79	$C_{24}H_{17}N_4O_2S_2$ (457.56)	63.00 (62.96)	3.75 (3.69)	12.24 (12.18)	14.02 (14.18)	3470, 3390, 3220, 3160 ($2NH_2$, NH) 1640 (C = O).	8.30–8.00 (br, 1H, NH), 7.50–7.30 (br, 10H arom), 4.10–3.30 (br, 4H, $2NH_2$),
6_d	**8/90**	289 – 90 (dioxan/ ethanol)	59	$C_{12}H_{11}N_6O_2S_2$ (335.39)	42.97 (42.88)	3.31 (3.29)	25.06 (25.02)	19.12 (19.30)	3480, 3416, 3330, 3190 ($4NH_2$, NH) 1635 (2C = O).	7.60 (s, 1H, NH), 6.90 (s, 2H, NH_2), 4.10 (s, 2H, NH_2), 3.80 (s, 4H, $2CONH_2$), 3.10
7_a	**6/75**	286 – 87 (dioxan/ DMSO)	78	$C_{18}H_{18}N_6O_4S_2$ (446.53)	48.42 (48.55)	2.29 (2.33)	18.82 (18.90)	14.39 (14.25)	3424, 3310, 3211 ($4NH_2$) 1715 (C = O).	7.30–7.10 (br, 4H,2 NH_2), 4.30–4.00 (q, 4H, $2CH_2$), 3.20 (s, 4H, $2NH_2$), 1.40–1.10
7_b	**5/80**	> 300 (DMSO/ ethanol)	64	$C_{14}H_8N_8S_2$ (352.40)	47.72 (47.65)	2.29 (2.25)	31.80 (31.69)	18.20 (18.36)	3410, 3315, 3206 ($4NH_2$), 2182 (2CN).	7.40–7.10 (br, 4H,2 NH_2), 4.20–3.80 (br, 4H, $2NH_2$).
7_c	**5/75**	206 – 08 (DMSO)	63	$C_{26}H_{18}N_6O_2S_2$ (510.62)	61.16 (61.20)	3.55 (3.58)	16.46 (16.55)	12.56 (12.43)	3410, 3283, 3184, ($4NH_2$) 1640 (C = O).	7.80–7.40 (m, 10H arom.), 7.30–7.10 (br, 4H, $2NH_2$), 3.70–3.30 (br, 4H, $2NH_2$).
7_d	**7/70**	> 300[e] (dioxan/ ethanol)	60	$C_{14}H_{12}N_8O_2S_2$ (388.43)	43.29 (43.32)	3.11 (3.13)	28.85 (28.90)	16.51 (16.43)	3440, 3370, 3319, 3186 ($6NH_2$), 1630 (C = O).	7.60–7.20 (br, 4H, $2NH_2$), 6.90–6.60 (br, 4H, $2NH_2$), 4.00–3.60 (br, 4H, $2CONH_2$).

Comp. No.	Reaction time h/temp. (°C)	M.P.[a] (Crys. Solvent)	Yield %	$M_F(M_w)$[b]	Analytical data calc. (Found) %				IR(Kbr) ν (cm^{-1})[c]	^{1}H-NMR (DMSO-d_6) (δppm)[d]
					C	H	N	S		
8	**5/reflux**	242–44 (DMSO/ ethanol)	58	$C_{10}H_4N_6Cl_2$ (279.09)	43.04 (43.00)	1.44 (1.42)	30.11 (30.04)	25.41(Cl) (25.49)	3370, 3312, 3184, ($2NH_2$) 2218 (2CN).	5.00–4.60 (br, 4H, $2NH_2$).
9	**12/80**	263–65 (DMSO/ ethanol)	63	$C_{18}H_{20}N_8O_4$ (412.41)	52.42 (52.50)	4.89 (4.92)	27.17 (27.08)	– –	3420, 3380, 3310, 3212 ($4NH_2$, 2NH), 1720 (C = O).	8.20–8.00 (br, 2H, 2NH), 7.20–6.80 (br, 4H, $2NH_2$), 4.20 – 3.80 (q, 4H, $2CH_2$),
10_a	**5/reflux**	> 300 (DMSO)	53	$C_{26}H_{20}N_8S_2$ (480.62)	64.98 (65.07)	4.19 (4.24)	17.49 (17.52)	13.34 (13.28)	3430, 3331, 3280, ($4NH_2$), 2205 (2CN).	6.70–6.40 (br, 4H, $2NH_2$), 4.40–3.90 (br, 4H, $2NH_2$), 2.90 (s, 2H, 2SH).
10_b	**6/reflux**	253–55 (DMSO)	58	$C_{26}H_{20}N_8S_2$ (508.63)	61.40 (61.48)	3.96 (3.99)	22.03 (22.10)	12.61 (12.49)	3399, 3314, 3311, ($4NH_2$).	8.00–7.50 (m, 10H arom.), 5.30–4.80 (br, 4H, $2NH_2$), 3.40–3.10 (br, 2H, NH_2), 1.30 (s, 2H, SH).
10_c	**11/reflux**	> 300[e] (acetic acid)	69	$C_{16}H_8N_8O_2S_2$ (408.42)	47.05 (47.11)	1.97 (2.00)	27.44 (27.50)	15.70 (15.62)	3410, 3318, 3208, ($2NH_2$, 2NH) 2205 (2CN), 1630 (C = O).	7.20–6.90 (br, 2H, 2NH), 3.80–3.40 (br, 4H, $2NH_2$), 2.80 (s, 2H, 2SH).

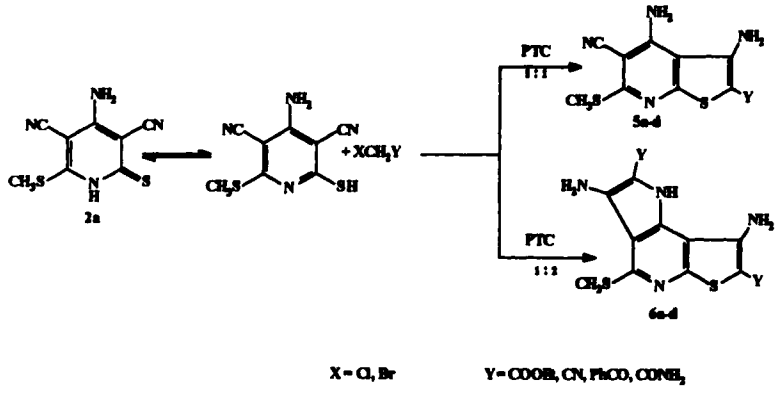
a. Uncorrected.
b. Satisfactory microanalyses; obtained; C, ± 0.3%, N, ± 0.4%, S, ± 0.2%.
c. Measured on Nicolet 710 FT-IR spectrophotometer.
d. Measured with a Varian EM 360L using TMS as internal standard.
e. Decomposed.

The formation sequence of **3** was confirmed by unsuccessful trial to prepare the compound $\mathbf{3_a}$ from $\mathbf{2_a}$ by its reaction with another mole of cyanothioacetamide under the same experimental conditions.

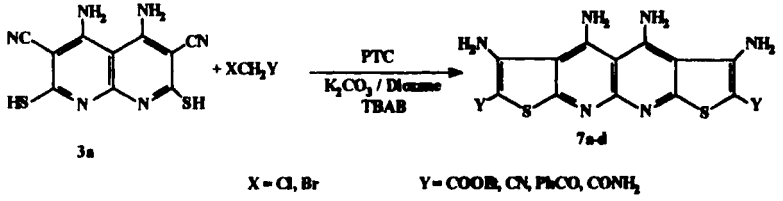
Compound **1** was treated with cyanoacetohydrazide in 1:1 or 1:2 molar ratio under PTC conditions to get the corresponding 1,2-diazepine or bis 1,2-diazepine $\mathbf{4_{a,b}}$ derivatives respectively in good yields. The IR and ^{1}H-NMR spectra of the products are in agreement with the proposed structures (c.f. Table I). .



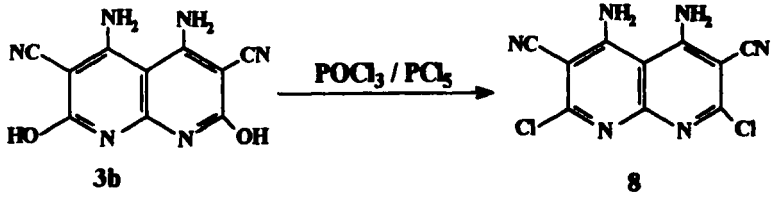
4-Amino-3,5-dicyano-6-methylmercapto-2-thione $\mathbf{2_a}$ was allowed to react with some reactive halo compounds, namely ethyl chloroacetate, chloroacetonitrile, phenacyl bromide or chloroacetamide in 1:1 or 1:2 molar ratio under PTC conditions [K_2CO_3/ dioxan / TBAB] at different temperatures and periods of time to give the corresponding thieno(2,3-b) pyridines $\mathbf{5_{a-d}}$ or pyrrolo(2,3-d)thieno(2,3-b)pyridines $\mathbf{6_{a-d}}$, respectively. IR and ^{1}H-NMR spectra are consistent with their structures. (c.f. Table I).



Using the PTC technique, compound $\mathbf{3_a}$ was investigated as a starting material for the synthesis of polyfused heterocyclic systems. Thus, when 4,5-diamino-3,6-dicyano-1,8-naphthyridine-2,7-dithiol $\mathbf{3_a}$ was treated with ethyl chloroacetate, chloroacetonitrile, phenacyl bromide or chloroacetamide in 1:2 molar ratio in K_2CO_3/ dioxan / in presence of tetrabutylammonium bromide catalyst, the corresponding bis(3-amino-2-substituted thieno)(2,3-b:2′,3′-b′)4,5-diamino-1,8-naphthyridines $\mathbf{7_{a-d}}$ were obtained.

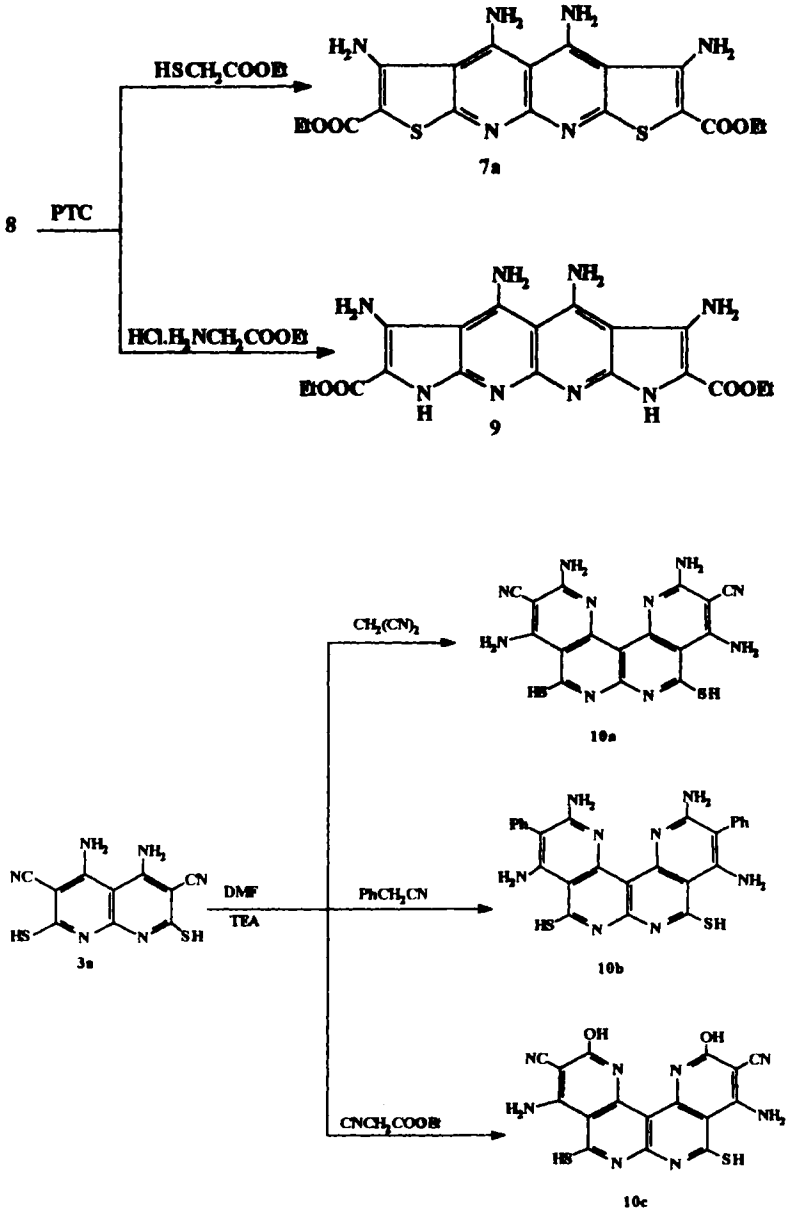


Chlorination of 4,5-diamino-3,6-dicyano-2,7-dihydroxy-1,8-naphthyridine $\mathbf{3_b}$ using a mixture of $POCl_3/PCl_5$ afforded the corresponding 4,5-diamino-2,7-dichloro-3,6-dicyano-1,8-naphthyridine **8**.



The reaction of compound **8** with ethyl mercaptoacetate or ethyl glycinate under PTC experimental conditions afforded compound $\mathbf{7_a}$ or bis(3-amino-2-carbethoxypyrrolo)(2,3-b:2′,3′-b′)4,5-diamino-1,8-naphthyridine **9**, respectively.

The reaction of compound $\mathbf{3_a}$ with active nitriles, namely malononitrile, phenylacetonitrile or ethyl cyanoacetate in 1:2 molar ratio in refluxing dimethyl formamide containing triethylamine gave the corresponding bis (2,4-diamino-3-substituted-5-thiol-1,6-naphthyridines) $\mathbf{10_{a-c}}$ (c.f. Table I).



EXPERIMENTAL

The MS were recorded on a Micromass 7070E spectrometer operating at 70eV, using direct inlet.

Synthesis of pyridines $2_{a,b}$, 1,8-naphthyridines $3_{a,b}$ and 1,2-diazepines $4_{a,b}$

General procedure

To a mixture of anhydrous potassium carbonate (3g), dry dioxan (40 ml), compound **1** (0.005 mol) and catalytic amount of tetrabutylammonium bromide (TBAB), was added 0.005 mole or 0.01 mole of cyanothioacetamide, cyanoacetamide or cyanoacetohydrazide. The reaction mixture was stirred over different periods of time at the appropriate temperatures (cf. Table I), till completion of the reaction (TLC). The reaction mixture was filtered off. The solid potassium carbonate was dissolved in distilled water (50 ml), filtered and the filtrate was acidified with acetic acid or hydrochloric acid (in case of compounds $\mathbf{2_a}$ and $\mathbf{3_a}$). The separated solid was collected by filtration and crystallized from the proper solvent (cf. Table I).

M.S: Compound $\mathbf{3_a}$: m/e (relative intensity) %: 274 (1.01), 237 (2.53), 222 (100), 205 (13.85), 189 (25.76), 176 (13.04).

M.S: Compound $\mathbf{3_b}$: m/e (relative intensity) %: 242 (1.27), 207 (13.82), 206 (100), 189 (41.52), 178 (11.44), 161 (14.64).

Synthesis of compounds 5_{a-d}, 6_{a-d} and 7_{a-d}

General procedure

0.005 Mole of compounds $\mathbf{2_a}$ or $\mathbf{3_a}$ was dissolved or suspended in 50 ml of dioxan and treated with 3 grams of anhydrous potassium carbonate, 0.005 mole or 0.01 mole of ethyl chloroacetate, chloroacetonitrile, phenacyl bromide or chloroacetamide and a catalytic amount of TBAB. The reaction mixture was stirred over periods of time and at different temperatures (Table I). At the end of the reaction, TLC, the organic layer was separated and evaporated in *vaccuo*. The residue was washed with light petroleum ether, collected by filtration and crystallized from the proper solvent (cf. Table I).

Synthesis of 4,5-diamino-2,7-dichloro-3,6-dicyano-1,8-naphthyridine 8

Compound $\mathbf{3_b}$ (0.005 mol) was refluxed with an excess amount of phosphorousoxychloride (20 ml) containing phosphorous pentachloride (2.5 g) for 5 hrs. The cooled reaction mixture was slowly added with stirring to an ice-cooled water whereby the product was separated out, and crystallized from DMSO/ethanol mixture.

Synthesis of bis(3-amino-2-carbethoxypyrrolo)(2,3-b:2′,3′b) 4,5-diamino-1,8-naphthyridine 9

The preceding phase transfer technique was used starting with compound **8** (0.002 mol) and ethyl glycinate hydrochloride (0.004 mol) in 30 ml dioxan. The product **9** was separated from dioxan layer and crystallized from DMSO/ethanol (cf. Table I).

Synthesis of compounds $\mathbf{10_{a\text{-}c}}$

General procedure

A mixture of compound $\mathbf{3_a}$ (0.002 mol) and (0.004 mol) of active nitriles, e.g. malononitrile, phenyl acetonitrile or ethyl cyanoacetate in dimethyl formamide (20 ml) containing triethylamine (0.5 ml) was refluxed for 5–11 hrs. The solvent was evaporated in *vaccuo* and the residue was diluted with distilled water and filtered. The separated solid was crystallized from the proper solvent to give compound $\mathbf{10_c}$, whereby the washing solution acidified with acetic acid, and the precipitant collected by filtration to give compound $\mathbf{10_{a,b}}$ then crystallized from the suitable solvent (cf. Table I).

References

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